

I2 --Figure 2 shows the cDNA sequence (SEQ ID NO: 8) and amino acid sequence (SEQ ID NO: 9) of human metalloproteinase inhibitor.--

Please replace the paragraph beginning at line 16 on page 6 with the following amended paragraph:

I3 --Figure 9 shows a synthetic DNA fragment (SEQ ID NOs: 35 and 36) constructed for use in the expression of recombinant human metalloproteinase inhibitor in E. coli, containing a ribosome binding site, an initiation methionine codon and codons for the first 42 amino acids of the mature protein.--

Please replace Table 4 on page 34 with the following amended Table 4:

--Table 4

I4 Amino-terminal sequence of bovine peak I-derived inhibitor

1	2	3	4	5	6	7	8	9	10	11	12	13
(Cys)	-Ser-	(Cys)	-Ser-	Pro-	Val-	His-	Pro-	Gln-	Gln-	Ala-	Phe-	(Cys) -
14	15	16	17	18	19	20	21	22	23	24	25	26
Asn-	Ala-	Asp-	Ile-	Val-	Ile-	Arg-	Ala-	Lys-	Ala-	Val-	Asn-	Lys-
27	28	29	30	31	32	33	34	35	36	37	38	39
Lys-	Glu-	Val-	Asp-	Ser-	Gly-	Asn-	Asp-	Ile-	Tyr-	Gly-	Asn-	Pro-
40	41	42	43	44	45							
Ile-	Lys-	Arg-	Ile-	Gln-	Tyr-	-----						

(SEQ ID NO: 10)--

Please replace Table 5 on page 35 with the following amended Table 5:

--Table 5

Cont
IS

Amino-terminal sequence of bovine peak II-derived inhibitor

1 2 3 4 5 6 7 8 9 10 11 12 13
(Cys)-Thr-(Cys)-Val-Pro-Pro-His-Pro-Gln-Thr-Ala-Phe-(Cys)-

14 15 16 17 18 19 20 21 22 23 24 25 26
Asn-Ser-Asp-Val-Val-Ile-Arg-Ala-Lys-Phe-Val-Gly-Thr-

27 28 29 30 31 32 33 34 35 36 37 38 39
Ala-Glu-Val-(Asn)-Glu-Thr-Ala-Leu-Leu-Tyr-Arg-Tyr-Leu-

40 41 42 43 44 45 46 47 48 49
Ile-Lys-Met-[Leu]-Lys-Met-Pro-Ser-[Gly]-Phe--- (SEQ ID NO: 11)--

Please replace Table 6 on page 37 with the following amended Table 6:

Comparison of the amino-terminal sequence of (1) human TIMP^a, (2) bovine peak II-derived inhibitor (TIMP)^b and (3) bovine peak I-derived inhibitor (MI)^c

	1	10	20
1 HUMAN TIMP	C T C V P P H P Q T A F C N S D L V I R		
2. BOVINE TIMP	C T C V P P H P Q T A F C N S D V V I R		
3 BOVINE MI	C S C S P V H P Q Q A F C N A D I V I R		
	21	30	40
1 HUMAN TIMP	A K F V G T P E V N Q T T L Y Q R Y E I		
2 BOVINE TIMP	A K F V G T A E V N E T A L L Y R Y L I		
3. BOVINE MI	A K A V N K K E V D S G N D I Y G N P I		

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1 HUMAN TIMP K M T K M Y K G F (SEQ ID NO: 12)

2 BOVINE TIMP K M (L) K M P S (G) F ... (SEQ ID NO: 13)

3 BOVINE MI K R I Q Y (SEQ ID NO: 14)

^a From Docherty et al., Nature, supra: and Carmichael et al., Proc.
Natl. Acad. Sci. USA, supra.

^{b,c} From sequence analyses described in Example 2.--

Please replace the paragraph on page 37, line 25, with the following amended paragraph:

--The amino acid composition of the bovine peak I-derived inhibitor (MI) is shown in Table 7. A sample of the peak I-derived inhibitor (1.2 ml; Table 1, step 2.1.3) was concentrated and introduced into 50 mM ammonium bicarbonate, pH 7.8 using an Amicon Centricon 10 ultrafiltration unit. The sample was then dried and subjected to amino acid composition analysis by the method described by Lu et al. (J. Chromatog. 368, 215-231 (1986)). This involved chromatographic analysis of phenylthiocarbamyl-amino acids generated after acid hydrolysis (24 h) of the samples. Data from three separate chromatographic analyses were used to estimate average residues per molecule values. For each of these analyses an amount of material derived from one-tenth of the starting sample was used. The value for total amino acids (178) used in calculating residues per molecule was taken from the gene-encoded sequence for the mature bovine MI (Example 3, Figure 1 (SEQ ID NO: 7)).--

Please replace the paragraph on page 39, line 17, with the following amended paragraph:

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I8

--5' GAT CAC AAT GTC AGC ATT GCA GAA GGC CTG CTG GGG ATG CAC AGG
3' (SEQ ID NO: 15)--

Please replace the paragraph beginning at line 24 on page 39 with the following amended paragraph:

I9

-- (T) (T) (T) (T)
5' GTC IAC (C)TC (C)TT (C)TT GTT IAC IGC (C)TT IGC 3' (SEQ ID NO:
16)--

Please replace the paragraph beginning at line 32 on page 39 with the following amended paragraph:

I10

-- (A) (A) (A) (A)
5' CTT IAT IGG (G)TT ICC (G)TA IAT (G)TC (G)TT ICC 3' (SEQ ID
NO: 17)--

Please replace the four paragraphs beginning at line 22 on page 41 with the following amended paragraphs:

I11

--probe 1
5' CGG GTC CTC GAT GTC CAG AAA CTC CTG CTT GGG GGG TGC TGC
TCC GCG GTA 3' (SEQ ID NO: 18)

probe 2

5' GAA CTT GGC CTG GTG TCC GTT GAT GTT CTT CTC CGT GAC
GTC CAT CCA 3' (SEQ ID NO: 19)

probe 3

5' CGC CTC ACA GCC CAT CTG GTA CCT GTG GTT CAG GCT CTT CTT
CTG GGT GGC 3' (SEQ ID NO: 20)

probe 4

5' GGG GTT GCC GTA GAT GTC GTT GCC AGA GTC CTC CTT CTT
ATT GAC TGC 3' (SEQ ID NO: 21)--

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Please replace the paragraph beginning at line 27 on page 43 with the following

amended paragraph:

I12

```
--ClaI                                     KpnI
5'  CGATTTGATTCTAGAAAGGAGGAATAACATATGGTTAACGCGTTGGAATTCGGTAC  3'
(SEQ ID NO: 22)
3'  TAAACTAAGATCTTCCTCCTTATTGTATACCAATTGCGCAACCTTAAGC      5'
(SEQ ID NO: 23)--
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Please replace the paragraph beginning at line 1 on page 44 with the following

amended paragraph:

I13

--The pL DNA sequence inserted is as follows:

AatII

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5'      CTAATTCGCTCTCACCTACCAAACAATGCCCCCTGCAAAAAATAAATTCATAT
3'  TGCAGATTAAGGCGAGAGTGGATGGTTTGTTACGGGGGGACGTTTTTTATTTAAGTATA

AAAAACATACAGATAACCATCTGCGGTGATAAATTATCTCTGGCGGTGTTGACATAAA
TTTTTTGTATGTCTATTGGTAGACGCCACTATTTAATAGAGACCGCCACAACCTGTATT

TACCACTGGCGGTGATACTGAGCACAT      3' (SEQ ID NO: 24)
ATGGTGACCGCCACTATGACTCGTGTAGC    5' (SEQ ID NO: 25)

                                   ClaI--
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Please replace the paragraph beginning at line 26 on page 51 with the following

amended paragraph:

I14

--(ii) A GPD- α -factor linker

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(Sau3A)                                met arg phe pro ser ile phe thr ala (SEQ ID
NO: 26)
GATCACACATAAATAAACAAAATG AGA TTT CCT TCA ATT TTT ACT GCA (SEQ ID
NO: 27)
TGTGTATTTATTTGTTTAC TCT AAA GGA AGT TAA AAA TG (PstI) (SEQ
ID NO: 28)--
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Please replace the paragraph beginning at line 1 on page 52 with the following

amended paragraph:

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I15 --(iv) A linker for joining the α -factor pre-pro leader to the α -factor terminator

sequence such as:

HindIII SphI SstI SmaI XhoI BglII (SalI)
AGCTTGCATGCGAGCTCCCCGGGCTCGAGATCTGATAACAACAGTGTAGATGTAACAAAA
(SEQ ID NO: 29)
ACGTACGCTCGAGGGGCCCGAGCTCTAGACTATTGTTGTCACATCTACATTGTTTTAGCT
(SEQ ID NO: 30)--

Please replace the paragraph beginning at line 1 on page 53 with the following amended paragraph:

I16 --II. A polylinker, whose sequence is shown below, was inserted into a EcoRI site of the modified 2 μ plasmid in (I) as shown in Figure 10(B.)

AATTC GATATC GAT GGTACC CGG GATCC GTCGAC AGATCT G (SEQ ID NO: 31)
G CTATAG CTA CCATGG GCC CTAGG CAGCTG TCTAGA CTAA (SEQ ID NO: 32)
EcoRI EcoRV ClaI KpnI SmaI BamHI SalI BglII EcoRI--

Please replace the paragraph beginning at line 21 on page 57 with the following amended paragraph:

I17 -- ClaI KpnI
5' CGATTTGATTCTAGAAGGAGGAATAACATATGGTTAACGCGTTGGAATTCGGTAC 3'
(SEQ ID NO: 33)
3' TAAACTAAGATCTTCCTCCTTATTGTATACCAATTGCGCAACCTTAAGC 5'
(SEQ ID NO: 34)--

Please replace the paragraph beginning at line 1 on page 66 with the following amended paragraph:

I18 --A sample of this human MI preparation (about 27 μ g) was subjected to amino-terminal amino acid sequencing through 20 cycles, using the methods described in Example 2. The initial yield was 923 pmol and the repetitive yield was 90-93%. The major sequence obtained exactly matched that predicted for mature human MI based

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